NAVAL HEALTH RESEARCH CENTER

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J. Fuller
K. Hanley
R. Schultz
M. Lewis
N. Freed
M. Ellis
V. Ngauy
R. Stoebner
M. A. K. Ryan
K. L. Russell

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NAVAL HEALTH RESEARCH CENTER
P. O. BOX 85122
SAN DIEGO, CA 92186-5122

BUREAU OF MEDICINE AND SURGERY (M2)
2300 E ST. NW
WASHINGTON, DC 20372-5300

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Julie Fuller[1]
LCDR Keith Hanley, MC, USN[2]
CAPT Robert Schultz, MC, USN[2]
LTC Michael Lewis, MC, USA[3]
Nicole Freed M.S.[1]
MAJ Michael Ellis, MC, USA[4]
CAPT Viseth Ngauy, MC, USAF[5]
LT Richard Stoebner, MC, USN[6]
CDR Margaret Ryan, MC, USN[1]
CDR Kevin Russell, MC, USN[1]

[1]Naval Health Research Center, P.O. Box 85122, San Diego, CA 92186-5122

[2]III Marine Expeditionary Force, Camp Courtney, Japan, FPO-AP 96606-5605

[3]Armed Forces Research Institute of Medical Sciences,
Bangkok, Thailand FPO-AP 96546-5000

[4]Brooke Army Medical Center, 3851 Roger Brooke Drive, Fort Sam Houston, TX 78234-6200

[5]Wilford Hall Medical Center, 759 MDOS/59/MDW/MMII,
2200 Bergquist Drive Suite 1, Lackland, AFB 78236;

[6]National Naval Medical Center, 8901 Wisconsin Avenue, Bethesda, MD

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Abstract

The Naval Health Research Center was charged with conducting laboratory-based surveillance for respiratory infections including severe acute respiratory syndrome (SARS), at the 2003 Cobra Gold Exercise in Thailand. SARS transmission was not known to be present in Thailand in early 2003, and there were concerns that exercise participants could bring SARS into the country. Respiratory illness surveillance was initiated, including geographic exposure history for elucidating a SARS “suspect” case. Although no suspect SARS cases were identified, 17 individuals met the case definition for febrile respiratory illness; diagnostic specimens were obtained from 16. Laboratory testing identified influenza A in 44%; selected sequence analysis demonstrated these were Fujian-like influenza strains, which was the predominant strain found globally in 2003/2004. Concern for SARS transmission was eased and knowledge of circulating respiratory pathogens was obtained as the logistics of implementing respiratory surveillance during a military training operation were overcome.

Introduction

The U.S. military is recognized for deploying its service members throughout nearly every continent in the world. Deployments range from small-scale training missions to politically and militarily significant exercises with myriad other worldwide joint and combined operational units. One of the largest combined exercises in the Pacific Command is Thailand's Cobra Gold. This multilateral exercise allows all military forces to work together in a joint/combined environment to conduct numerous operations on land, at sea, and in the air. The exercise commenced in 1982 with the U.S. and Thai militaries. In 2000, Singapore's armed forces joined the exercise. As of 2003, 11 other countries from the Pacific region participated. The 2003 Cobra Gold exercise included approximately 12,000 troops from participating nations, with 5,200 of those being of the U.S. Armed Forces. The overall purpose for Cobra Gold is to improve U.S., Thai, and Singapore combat readiness and combined joint interoperability, enhance security relationships, and to demonstrate U.S. determination in the region. The specific focus of the 2003 exercise was to enhance peace enforcement, humanitarian assistance, and disaster relief operations.[1]

As plans for Cobra Gold 2003 were unfolding, however, the world was anxiously watching the spread of another powerful force. In February 2003, an atypical pneumonia with high mortality was seen in the Guangdong province of China and reported by the Chinese Ministry of Health. Later called severe acute respiratory syndrome (SARS), a newly recognized, highly pathogenic strain of coronavirus (SARS-CoV) was found to be causal. Respiratory illnesses caused by viruses in the family Coronaviridae have long been recognized.[2-13] Two species known to cause human

illness, OC43 and 229E, were first described in 1965.[14] The burden of these viruses in U.S. military populations was described in 1974 at Marine Corps recruit training centers in the United States, causing an infection rate of 0-5 per 100 cases in non-outbreak years.[15] In contrast to these coronaviruses, however, SARS-CoV is quite distinct at the genome level and the mortality associated with it is much different.[16] Before the spread of the virus abated in August 2003, 8422 cases from 29 countries were reported with 916 fatalities. “Hot zones,” regions where active transmission was occurring, were mainland China, Hong Kong, Canada, Singapore, Vietnam, and later Taiwan, as recognized by the World Health Organization (WHO).[7,11,12] Further limited transmission has been observed in 2004.[17]

Although SARS transmission was not recognized in the country of Thailand prior to Cobra Gold 2003, a small number of imported cases, which were contained, were seen in the country. The Kingdom of Thailand was concerned about, and the U.S. military was sensitive to, the potential for participants to pass through or come from countries with known SARS transmission. The Naval Health Research Center (NHRC) has an 8-year history of surveillance and diagnosis of febrile respiratory illness (FRI) within active-duty forces. Recently, these capabilities and resources were extended to select deployed forces and ships. Given our capabilities and presence within our deployed forces, NHRC was tasked with conducting laboratory-based active surveillance for respiratory illness, including SARS, during the exercise, with the intent of early recognition and response.[18,19]

Methods

Respiratory surveillance was conducted during Cobra Gold 2003 by NHRC, with coordination and logistic support through the Armed Forces Research Institute for Medical Sciences (AFRIMS), a joint U.S. Army–Royal Thai Army research facility located in Bangkok since 1958. For many years, AFRIMS has conducted routine diarrhea surveillance during Cobra Gold, and researchers were able to easily accommodate respiratory surveillance into this exercise. In addition to the support received by AFRIMS, two main appointed medical care units and numerous U.S. aid stations assisted in conducting this surveillance. The two medical care units, Fort Thanarat (located in the Hua Hin area, southwest of Bangkok), and Camp Samae San (located in Pattaya Beach, southeast of Bangkok) were selected due to their centralized locations to the U.S. military forces. Individual U.S. aid stations were sent notification of the surveillance, along with detailed reporting methods and instructions to send all patients meeting the FRI case definition to Fort Thanarat or Camp Samae San. The FRI case definition was oral temperature $\geq$100.5°F and a respiratory symptom (cough, sore throat, shortness of breath, or difficulty breathing), or any diagnosed pneumonia.

Supplies, including viral transport media, swabs (sterile Dacron), preprinted subject identification labels, FRI log sheets, and informed consent/case forms were provided to both units. Prior to the commencement of the exercise, an NHRC representative conducted training on data and specimen collection procedures. To record the number of personnel under surveillance and the number of those who presented with FRI symptoms, the clinicians at each medical care unit completed a daily

summary form. Individuals who presented meeting the case definition of FRI were asked to complete an informed consent/case form and to permit a throat swab. When a patient meeting the above case definition answered “yes” to either of the following questions, the patient was also considered a “suspect” SARS case,[5] and placed in respiratory isolation pending outcome of immediate evaluation:

1. Has the patient traveled, within 10 days prior to onset of symptoms, to mainland China, Hong Kong, or Singapore?

Or

2. Has the patient had close contact within 10 days of onset of symptoms with a person known to be a suspect severe acute respiratory syndrome (SARS) case?

Additional specimens and immediate testing were required for all suspect SARS cases. For all other cases, diagnostic specimens were collected with a sterile Dacron swab and placed directly into viral transport media. A preprinted subject identification label was placed on the vial and immediately placed in a –70°C freezer or liquid nitrogen tank. An identical preprinted label was placed on the case report form, and the FRI log sheet. Once the exercise ended, Samae San and Thanarat transported the specimens to AFRIMS, and shipment to the NHRC Respiratory Disease Laboratory was arranged.

Samples received at the NHRC Respiratory Disease Laboratory were processed in both the classic virology laboratory using cell culture techniques (A549 and RMK cells), and in the molecular laboratory using standard polymerase chain reaction (PCR)

and reverse transcriptase (RT) PCR methods. Testing was performed for the following pathogens: influenza A, influenza B, adenovirus, parainfluenza viruses 1-3, enteroviruses, coronaviruses (229E and OC43), rhinovirus, and human metapneumovirus. All positives for influenza A were typed by 4 additional primer sets (N1, N3, H1, H3). A portion of the H3 gene was sequenced on the influenza A positive samples. Since viral transport media were used to collect the specimens, no testing was conducted for bacterial pathogens. If SARS-CoV testing had been required, NHRC would have used the real-time RT-PCR assay developed by the Centers for Disease Control and Prevention (CDC), with validation by CDC.[20]

Results

The number of troops under surveillance during the exercise was estimated to average 4,800 over a 3-week period; 17 patients were seen who met the case definition, for an attack rate of 0.12 FRI cases per 100 recruit-weeks. Sixteen of the 17 patients gave a diagnostic specimen. The demographics of these 16 individuals were average age 27 years, all were male, 7 were U.S. Marine Corps, 7 were U.S. Army, 1 was U.S. Air Force, and 1 not determined. The average symptom duration was 3.7 days, and only 1 of the 16 patients was hospitalized with pneumonia. None had a history of asthma, and all but 1 was vaccinated with the influenza vaccine within the last 12 months (2 unknown).

Of the 16 diagnostic specimens received, 7 (44%) tested positive for influenza A, 2 (13%) for coronavirus OC43, 2 (13%) for respiratory syncytial virus, 1 (6%) rhinovirus,

and 4 (25%) were negative. None met the case definition for a suspect SARS case during the surveillance, so patient isolation and urgent investigations were not required.

Of the influenza A isolates sequenced, all were found to be closely related to the Fujian strain (Fig. 1), which was the predominant influenza strain seen globally in the recent 2003/2004 influenza season.[21,22] Low numbers of this strain were seen in the 2002/2003 influenza season in the United States but the Panama/2007/99 strain was predominant at that time.[23] CDC and WHO knew that the Fujian-like strain would potentially dominate the 2003/2004 influenza season, however it could not be grown to adequate titers in time to be included in the 2003/2004 influenza vaccine. It was suspected that the Panama/2007/99 strain, included in the vaccine, would provide at least partial coverage for the circulating Fujian-like strain.[24] Studies are still currently under way to determine the effectiveness of the 2003/2004 influenza vaccine against the Fujian-like strain.[22]

Conclusion

In addition to the human cost of SARS, the economic cost of SARS on the Asian and world economies was on the order of tens of billions of dollars ($18 billion by one estimate).[25]

The Government of Thailand was extremely nervous that the large influx of personnel who may have traveled through high SARS transmission regions represented both a health and economic threat to the Kingdom of Thailand. The ability to conduct this high priority surveillance was a critical factor in reassuring the Thai government that U.S. forces participating in Cobra Gold 2003 did not represent an uncontrolled health

threat. In the process, important data on agents causing respiratory illness during the exercise were collected, and concern for SARS transmission was eased as the logistics of implementing respiratory surveillance during a military operation were overcome.

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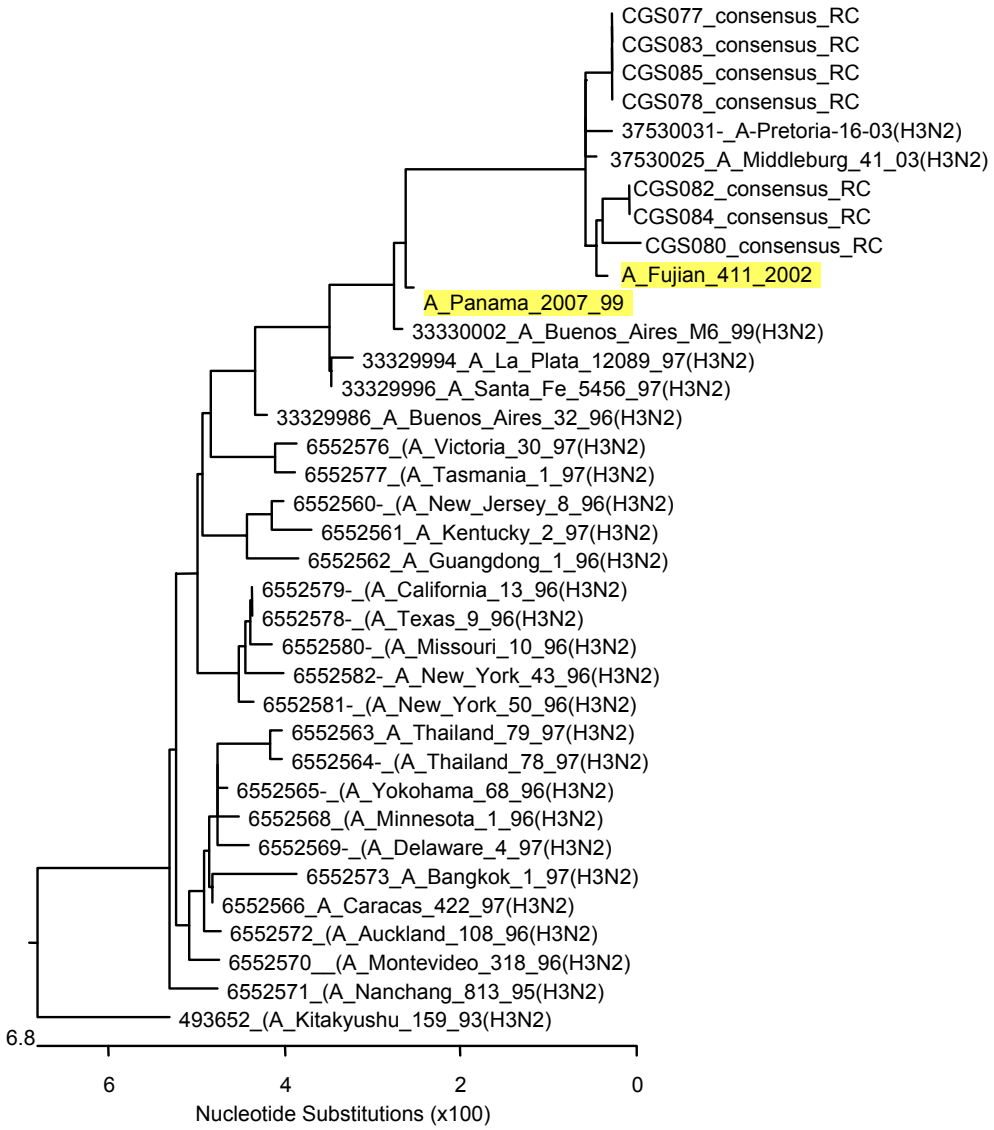
Fig. 1. Phylogenetic tree for the influenza A isolates from Cobra Gold Exercise 2003.



Cobra Gold specimens noted with the CG prefix
Phylogenetic tree using Neighboring Joining method, ClustalW alignment

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6. AUTHORS
Julie Fuller; LCDR Keith Hanley, MC, USN; CAPT Robert Schultz, MC, USN; LTC Michael Lewis, MC, USA; Nicole Freed M.S.; MAJ Michael Ellis, MC, USA; CAPT Viseth Ngauy, MC, USAF; LT Richard Stoebner, MC, USN; CDR Margaret Ryan, MC, USN; CDR Kevin Russell, MC, USN

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14. ABSTRACT (maximum 200 words)

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